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Effects of a 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitor, Fluvastatin, on Coronary Spasm After Withdrawal of Calcium-Channel Blockers

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Objectives The purpose of this study was to determine whether a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) suppresses coronary spasm.

Background Coronary spasm is associated with endothelial dysfunction. Statins have been shown to improve endothelial function.

Methods This was a prospective, randomized, open-label, end point study. Sixty-four patients who had no significant organic coronary stenosis and in whom coronary spasm was induced by intracoronary injection of acetylcholine (ACh) were randomly assigned to fluvastatin 30 mg/day plus the conventional calcium-channel blocker (CCB) therapy (31 patients, statin group) or the conventional CCB therapy (33 patients, nonstatin group). After 6 months of treatment, the intracoronary injection of ACh was repeated and the coronary spasm was assessed.

Results Coronary spasm was suppressed in 16 of the 31 patients (51.5%, $p < 0.0001$) of the statin group and in 7 of the 33 patients (21.2%, $p = 0.0110$) of the nonstatin group after 6 months of treatment. Thus, the number of patients with ACh-induced coronary spasm was significantly reduced in the statin group as compared with the nonstatin group (51.6% vs. 21.2%, $p = 0.0231$) after 6 months of treatment.

Conclusions The addition of fluvastatin 30 mg/day to the conventional CCB therapy for 6 months significantly reduced the number of patients with ACh-induced coronary spasm as compared with the conventional CCB therapy. Thus, a statin (fluvastatin) may possibly be a novel therapeutic drug for coronary spasm. (J Am Coll Cardiol 2008;51:1742–8) © 2008 by the American College of Cardiology Foundation

It is established that coronary spasm plays an important role not only in the pathogenesis of variant angina but also in ischemic heart disease in general, including resting angina, effort angina, acute myocardial infarction, and sudden death (1,2). Calcium-channel blockers (CCBs) have been shown to be highly effective in suppressing coronary spasm and are widely used as the standard therapy for coronary spasm (1–4). However, a substantial number of patients with coronary spasm are resistant to CCBs even in high doses, and lethal arrhythmias and/or sudden death occur in some of them (1). We have shown that endothelial nitric oxide (NO) activity is reduced and endothelial function impaired in the coronary arteries involved in spasm (1,5). There is increasing evidence that 3-hydroxy-3-methylglutaryl coen-

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zyme A reductase inhibitors (statins) improve endothelial dysfunction and reduce cardiovascular events in patients with coronary artery disease (6–9). Thus, it is possible that statins may also suppress coronary spasm and prove to be a novel therapy for coronary spasm. However, no studies have been done to test this hypothesis.

The present study was designed to examine whether addition of a statin to the conventional CCB therapy would result in greater reduction in coronary spasm as compared with the conventional CCB therapy.

Methods

Patients. The SCAST (Statin and Coronary Artery Spasm Trial) trial was a prospective randomized open-label end point study to examine the effect of a statin (fluvastatin) added to the conventional therapy on coronary spasm. We recruited 78 participants between January 2002 and December 2005 from 9 hospitals in Japan. Entry criteria were subjects who were 30 to 80 years of age who underwent coronary angiography because of chest pain and/or ischemic ECG changes on exercise and had no organic coronary stenosis (>50%) and in whom coronary spasm was induced by intracoronary injection of acetylcholine (ACh). Coronary spasm was defined as a total or subtotal obstruction or severe diffuse constriction of an epicardial coronary artery associated with transient myocardial ischemia as evidenced by ischemic ST-segment changes on ECG. Exclusion criteria included recent myocardial infarction, acute coronary syndrome, heart failure, liver disease, creatinine level >1.5 mg/dl, acute inflammation, malignant diseases, and cholesterol-lowering medication within a month. These 78 patients were registered and randomly assigned to either the statin group (fluvastatin 30 mg/day plus conventional therapy, n = 39) or the nonstatin group (conventional therapy, n = 39) by using a random number generating computer system. The conventional therapy consisted of CCBs (slow-release diltiazem 100 to 200 mg/day, or slow-release nifedipine 20 to 40 mg/day). The protocol of this study was approved by all site institutional review boards and each patient provided written informed consent.

Induction of coronary spasm. Coronary spasm was induced by intracoronary injection of ACh after diagnostic catheterization in the morning. The details of the method were previously reported (10). In brief, nitrates, CCBs, beta-adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and other vasodilators or vasoconstrictors were withheld for >48 h. ACh was injected in incremental doses of 50 and 100 μg into the left coronary artery and then 50 μg into the right coronary artery under continuous monitoring of ECG and blood pressure. Coronary spasm induced by this method usually disappeared spontaneously within 1 to 2 min, and both the left and right coronary arteries could be examined separately unless severe spasm occurred in the left coronary artery and necessitated the prompt injection of isosorbide dinitrate into the artery. After the end of the test, isosorbide dinitrate (0.1 mg) was injected into the coronary artery and angiography was again performed.

Abbreviations and Acronyms

ACh = acetylcholine
CCB = calcium-channel blocker
ECG = electrocardiogram
LCA = left coronary artery
LDL = low-density lipoprotein
NO = nitric oxide
RCA = right coronary artery
ROCK = RhoA-associated kinase

Treatment and follow-up. Each patient was evaluated at 1, 3, and 6 months for assessment of angina episodes, drug compliance, ECG, lipid profile, and safety markers. At the 6-month follow-up, patients again underwent catheterization after withdrawal of CCBs for a week in both groups, but the statin was not withdrawn in the statin group. Care was taken to replicate angiographic views, tube height, catheter positions, and order of infusions used in the baseline study.

Assessment of coronary artery diameter and ECG changes in response to ACh injection. Severe coronary spasm to a residual lumen diameter <0.4 mm could not be accurately quantified because of technical limitations of the computer-assisted quantitative coronary angiography (11). However, the spasm sites at baseline were identified and the same segments and the nonspasm segments proximal to the spasm sites were evaluated quantitatively at the submaximal dose of ACh (50 μg) in the left coronary artery at baseline and follow-up at the core laboratory. Each segment was referenced to a specific anatomic landmark for identification and films from the baseline and follow-up were examined at the same time to ensure analysis of the identical portion of the vessel. The measurement was blinded to the ECG findings and the group assignment. An end-diastolic frame was digitized and the diameter of the index vessel was measured with CAAS II software (PIE Medical Imaging, Maastricht, Limburg, the Netherlands). Two or 3 sites of each segment were measured and the coronary response to ACh was expressed as the percentage change from baseline in mean lumen diameter and was compared at the same site of the same artery in the same patients before and after 6 months of treatment in each group. The ECG was examined in a blinded fashion as to the coronary angiographic findings and the group assignment at the core laboratory.

Laboratory methods. Fasting blood samples were drawn by venipuncture 1 to 2 days before coronary angiography and the hematological and biochemical analyses were done using standard laboratory procedures. Serum high sensitivity C-reactive protein was measured in duplicate by automated immunoturbidimetric assay using the Synchron LX20 Pro system (Beckman Coulter, Inc., Fullerton, California) (12).

Statistical analysis. The primary end point of the study was the ACh-induced coronary spasm 6 months after the treatment. We hypothesized that the induction rate of coronary spasm in the statin group would be different from that in the nonstatin group. The number of sample size

(number of patients) (n = 76 to 78) was calculated based on a z test at the 2-tailed test 5% significance level and 80% power. A 30% treatment effect was considered to be clinically significant, assuming a recurrence rate of coronary spasm to be 80% to 90% in the nonstatin group. The secondary end point was the coronary artery diameter change in response to the submaximal dose (50 μg) of ACh. For continuous variables, differences between groups were evaluated by unpaired t test or Mann-Whitney rank-sum test, and those within groups by paired t test or Wilcoxon signed rank test. For discrete variables, differences were expressed as counts and percentages and were analyzed with chi-square (or Fisher exact) test between groups and with McNemar test or Fisher exact test within groups, as appropriate. A 2-tailed p value of <0.05 was considered to be statistically significant. Data were expressed as mean ± SD. However, when the variable was significantly skewed, the median (25th, 75th percentile) was reported.

This study was investigator initiated and the drug makers had no direct or indirect involvement in the design of the study, provision of the drug, data collection, or preparation of the manuscript.

Results

Clinical characteristics and adverse events. Of the 78 patients randomized, 14 patients were withdrawn (statin group: n = 8; nonstatin group: n = 6). In the statin group, 1 patient suffered from sudden death during an earthquake, 1 patient from drug allergy, and 1 patient underwent a cervical operation. In the nonstatin group, 1 patient could not undergo coronary angiography at 6-month follow-up because of trouble at catheterization. The remaining patients were withdrawn due to unwillingness to undergo the second catheterization (statin group: n = 5; nonstatin group: n = 5). Thus, a total of 64 patients (31 patients in the statin group and 33 patients in the nonstatin group) were available for analysis, and all of these patients had adhered to the protocol. The baseline characteristics of the 2 treatment groups are shown in Table 1.

Twenty-eight patients of the statin group and 27 patients of the nonstatin group had episodes of chest discomfort before the entry. Twenty-one of the patients (75.0%, $p < 0.0001$) in the statin group and 19 of the patients (70.4%, $p < 0.001$) in the nonstatin group became asymptomatic during 6 months of treatment. Thus, CCBs were

Table 1 Clinical Characteristics of the Study Subjects

Variables	Statin Group (n = 31)	Nonstatin Group (n = 33)	p Value
Age (yrs)	63.4 ± 12.5	61.8 ± 10.2	0.6091
Gender (male/female)	21/10	18/15	0.2795
Body mass index (kg/m^2)	23.6 ± 3.4	24.5 ± 3.7	0.3022
Hypertension	10/31	14/33	0.4012
Diabetes mellitus	6/31	6/33	0.9044
Current smoker	15/31	12/33	0.3304
Leukocyte (/μl)	6,425 ± 1,582	6,228 ± 2,049	0.6689
Hemoglobin (g/dl)	13.4 ± 1.7	13.6 ± 1.7	0.6382
Platelet ($\times 10^4/\mu$l)	22.8 ± 6.0	22.2 ± 8.3	0.7546
CRP (mg/l)*	1.94 (0.79, 5.04)	1.36 (0.38, 2.45)	0.3502
Total protein (g/dl)	6.8 ± 0.5	6.8 ± 0.4	0.8798
Albumin (g/dl)	3.98 ± 0.41	3.97 ± 0.33	0.8989
Fast blood sugar (mg/dl)	104.3 ± 22.7	111.2 ± 39.8	0.4082
AST (U/l)	25.3 ± 11.1	24.9 ± 9.3	0.8818
ALT (U/l)	25.6 ± 14.7	25.7 ± 17.1	0.7874
CPK (U/l)	113.0 ± 75.4	101.5 ± 63.2	0.5154
Total cholesterol (mg/dl)	193.8 ± 36.3	193.9 ± 44.2	0.9950
LDL cholesterol (mg/dl)	114.9 ± 33.2	119.7 ± 27.0	0.5366
HDL cholesterol (mg/dl)	55.5 ± 13.8	53.3 ± 15.1	0.5656
Triglyceride (mg/dl)	130.2 ± 67.0	134.3 ± 64.7	0.8021
Medications			
Ca-channel blockers	31/31	33/33	0.9642
Diltiazem/nifedipine	20/11	26/7	0.3778
Aspirin	11/31	13/33	0.7468
ACE inhibitor	3/31	2/33	0.6673
ARB	6/31	10/33	0.3121
Nitrate	4/31	7/33	0.5119
Beta-blocker	1/31	3/33	0.6136
Fibrate	1/31	0/33	0.4844

*Median (25th, 75th percentile).

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin II receptor blocker; AST = aspartate aminotransferase; CPK = creatine phosphate kinase; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

highly effective in suppressing symptomatic coronary spasm in both groups in agreement with the results of previous studies (1–4), and there was no significant difference (p = 0.924) in the incidence of subjective symptoms during the treatment period between the 2 groups with these sample sizes. Twenty-five patients in the statin group and 22 patients in the nonstatin group underwent 24-h Holter monitoring on entry, and ischemic ECG changes were detected in 6 patients (24.0%) of the statin group and in 5 patients (22.7%) of the nonstatin group. After 6 months of treatment, ischemic ECG changes on Holter monitoring were detected in none of the statin group and in 2 patients of the nonstatin group. No adverse effects were detected in either group during the follow-up period.

Coronary angiographic and ECG changes in response to ACh at baseline and after 6 months of treatment. At the registration, spasm was induced at 26 left coronary artery (LCA) and at 19 right coronary artery (RCA) in the statin group, and at 27 LCA and at 16 RCA in the nonstatin group, accompanied by ischemic ECG changes as shown in Table 2. After 6 months of treatment and after withdrawal of CCBs for 1 week, spasm was induced at 12 LCA and at 10 RCA in the statin group, and at 21 LCA and at 13 RCA in the nonstatin group, accompanied by ST-segment changes as shown in Table 2. The ACh-induced coronary spasm after 6 months of treatment was similar to that of the baseline in location and type (total or subtotal obstruction, or severe diffuse narrowing).

Coronary spasm was suppressed in 16 out of 31 patients (51.6%, p < 0.0001) of the statin group and in 7 out of 33 patients (21.2%, p = 0.0110) of the nonstatin group after 6 months of treatment. Thus, the number of patients with ACh-induced coronary spasm was significantly reduced in the statin group as compared with the nonstatin group (51.6% vs. 21.2%, p = 0.0231) after 6 months of treatment (Fig. 1). The results also revealed that coronary spasm was induced in a high proportion of the patients after withdrawal of CCBs after 6 months of treatment.

Quantitative angiographic analysis showed that vasoconstrictor response (percent change in luminal diameter) to 50 μg ACh of the LCA at the same spasm segment of the same patient was significantly reduced in both groups after 6 month as compared with at baseline (from −35.5 ± 20.1% to −21.3 ± 16.9%, p < 0.0001 in the statin group, and from −36.8 ± 21.6% to −30.1 ± 26.3%, p = 0.0221 in the nonstatin group). There was thus a significant reduction in the constrictor response to ACh in the statin group as compared with the nonstatin group (−21.3 ± 16.9% vs. −30.1 ± 26.3%, p = 0.0087) after 6 months of treatment (Fig. 2 left). However, there was no significant difference in the response at the nonspasm segments between the 2 groups (−6.6 ± 12.6% in the statin group vs. −10.3 ± 12.8% in the nonstatin group, p = 0.1029) after 6 months of treatment, although the response was significantly reduced in the statin group (p = 0.0337) after 6 months of treatment (Fig. 2, right).

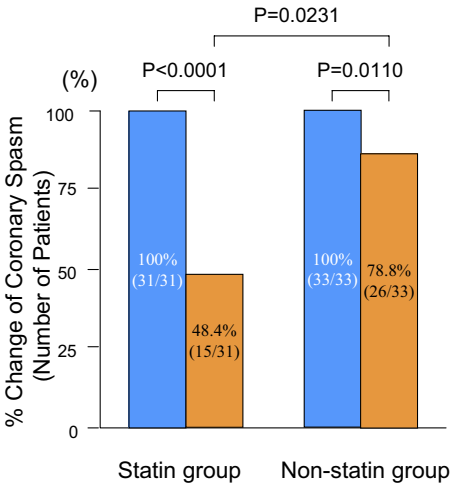

Figure 1 **Statin and ACh-Induced Coronary Spasm**

Number of patients with acetylcholine (Ach)-induced coronary spasm at baseline **(blue bars)** and after 6 months **(orange bars)** of treatment in the statin group and nonstatin group.

Lipid profile and other laboratory data. The results of lipid and other laboratory data are shown in Table 3. The levels of low-density lipoprotein (LDL) cholesterol and C-reactive protein decreased significantly in the statin group (from 114.9 ± 33.2 mg/dl to 86.4 ± 27.6 mg/dl, p < 0.0001, and from 1.94 [0.79, 5.04] mg/l to 0.60 [0.25, 2.20] mg/l, p = 0.0077, respectively), whereas there were no differences in these levels in the nonstatin group, after 6 months of treatment.

Table 2 **Ischemic ECG Changes Accompanying ACh-Induced Coronary Spasm at Baseline and After 6 Months of Treatment**

		Statin Group			Nonstatin Group		
	ECG Changes	Baseline	6 Months	p Value	Baseline	6 Months	p Value
LCA	ST-segment elevation	11/26 (42.3%)	3/26 (11.5%)		9/27 (33.3%)	6/27 (22.2%)	
	ST-segment depression	15/26 (57.7%)	9/26 (34.6%)		18/27 (66.7%)	15/27 (55.6%)	
	Total	26/26 (100%)	12/26 (46.2%)	< 0.0001	27/27 (100%)	21/27 (77.8%)	0.0229
RCA	ST-segment elevation	10/19 (52.6%)	5/19 (26.3%)		6/16 (37.5%)	5/16 (31.3%)	
	ST-segment depression	9/19 (47.4%)	5/19 (26.3%)		10/16 (62.5%)	8/16 (50.0%)	
	Total	19/19 (100%)	10/19 (52.6%)	< 0.0001	16/16 (100%)	13/16 (81.3%)	0.2258

ACh = acetylcholine; ECG = electrocardiogram; LCA = left coronary artery; RCA = right coronary artery.

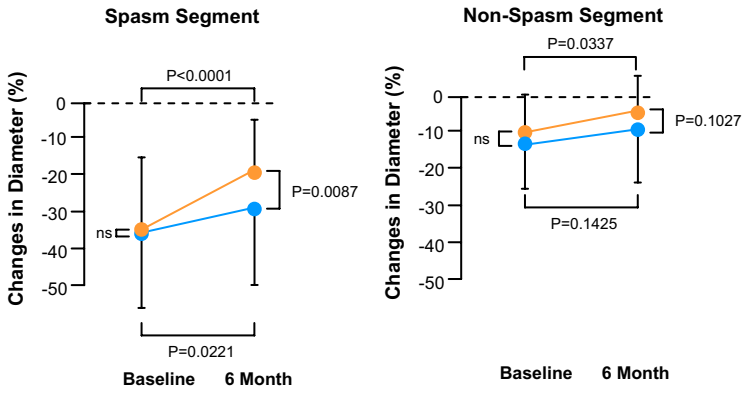

Figure 2 Coronary Artery Diameter Change to ACh Injection

Response of coronary artery diameter to intracoronary injection of acetylcholine (ACh) (50 μg) at baseline and after 6 months of treatment at the spasm segment **(left)** and the nonspasm segment **(right)** in the statin group (**orange**; n = 63) and nonstatin (**blue**; n = 66) group.

Discussion

Calcium-channel blockers are established as the standard therapy for coronary spasm (1,3,4). However, coronary spasm may not be completely controlled even with high doses of CCBs in a substantial number of patients (1,3,4). Moreover, it is not known how long the drugs should be administered for control of coronary spasm (13,14). Coronary spasm occurs most often from midnight to early morning and is often silent and is usually not induced by exercise in the daytime (1,14). Moreover, there are daily, weekly, and monthly, as well as circadian, variations in the frequency of coronary spasm (1,15,16) and the episodes of coronary spasm may not be detected even with 24-h ambulatory ECG monitoring as shown in this as well as previous studies (1,15). Accordingly, we examined the effect of a statin (fluvastatin) on the coronary spasm induced by the intracoronary injection of ACh in the present study.

The study showed that the addition of fluvastatin to the conventional therapy for 6 months significantly reduced the occurrence of coronary spasm as compared with the conventional therapy. The quantitative angiographic analysis also showed that the constrictor response to a submaximal dose of ACh at the same site of the same spasm segment was reduced significantly in the statin group as compared with the nonstatin group, but there was no significant difference in the response at the same site of the nonspasm segment between the 2 groups after 6 months of follow-up. Thus, the present study reveals that the spasm segment was specifically responsive to a statin (fluvastatin) as compared with the nonspasm segment. Fluvastatin significantly reduced the serum level of LDL cholesterol. However, it is not known whether the suppression of coronary spasm was directly caused by the lowering of LDL cholesterol. Our previous study shows that elevation of LDL cholesterol is not a risk factor for coronary spasm (17). Recent experimental and clinical evidence indicates that statins improve endothelial dysfunction and suppress inflammation independently of cholesterol lowering or through "pleiotropic" effects (8,9,18,19). We have shown that endothelial NO bioactivity was reduced and levels of markers of inflammation were increased in patients with coronary spasm (1,5,15,20). In the present study, the serum level of C-reactive protein, a marker of inflammation was reduced significantly in the statin group, whereas the level remained unchanged in the nonstatin group in agreement with the results of previous studies (8,9,21,22).

Table 3 Lipid Profile and Other Laboratory Data at Baseline and After 6 Months of Treatment

	Statin Group (n = 31)			Nonstatin Group (n = 33)		
Variables	Baseline	6 Months	p Value	Baseline	6 Months	p Value
Total-cholesterol (mg/dl)	193.8 ± 36.3	167.7 ± 35.3	<0.0001	193.9 ± 44.2	206.9 ± 26.5	0.0767
LDL cholesterol (mg/dl)	114.9 ± 33.2	86.4 ± 27.6	<0.0001	119.7 ± 27.0	117.1 ± 29.5	0.6124
HDL cholesterol (mg/dl)	55.5 ± 13.8	59.6 ± 13.9	0.0371	53.3 ± 15.1	54.6 ± 17.7	0.8151
Triglyceride (mg/dl)	130.2 ± 67.0	113.5 ± 63.1	0.1155	134.3 ± 64.7	150.3 ± 124.7	0.4491
CRP (mg/l)*	1.94 (0.79, 5.04)	0.60 (0.25, 2.20)	0.0077	1.18 (0.38, 2.45)	0.61 (0.20, 1.40)	0.4503
Platelet ($\times 10^4/\mu l$)	22.8 ± 6.0	21.6 ± 5.6	0.0363	22.2 ± 8.3	23.8 ± 8.8	0.2190

*Median (25th, 75th percentile).
Abbreviations as in Table 1.

In addition to inhibiting cholesterol synthesis, statins are shown to block the synthesis of isoprenoid intermediates of the cholesterol biosynthetic pathway, thereby preventing translocation and activation of RhoA (8,19). Emerging evidence indicates that inhibition of RhoA and its downstream RhoA-associated kinase (ROCK) pathway leads to the elevation of endothelial NO synthase expression and NO activity in conjunction with reduction of inflammation, as well as proliferation of vascular smooth muscle (8,18,19).

Coronary spasm may be regarded as an abnormal hypercontraction of coronary vascular smooth muscle and accumulating evidence indicates that hypercontraction of vascular smooth muscle is mainly caused by the enhanced Ca^{2+} sensitization through the activation of the RhoA/ROCK pathway (23–25).

Accordingly, it is reasonable to postulate that the Rho/ROCK pathway plays a key role in the pathogenesis of coronary spasm (24,25) and statins, including fluvastatin are likely to suppress coronary spasm by inhibiting the Rho/ROCK pathway, thereby improving endothelial function, enhancing NO activity, and suppressing inflammation and Ca^{2+} sensitivity of coronary smooth muscle. Indeed, we and others (18,26–28) have shown that statins enhance the expression of endothelial NO synthase gene in human endothelial cells. The present study thus suggested that a statin may be a novel disease-modifying drug for coronary spasm based on the underlying pathogenesis and improve the overall prognosis for the patients. On the other hand, coronary spasm was again induced in the majority of the patients on withdrawal of CCBs after 6 months of treatment without a statin. The results indicated that calcium-channel blockade for 6 months might not substantially modify the underlying pathogenesis of coronary spasm in the majority of the patients (15) and revealed that CCBs should not be withdrawn for at least 6 months.

One previous study reported that a statin reduced coronary vasoconstrictor response to ACh, reflecting improved endothelial function in patients with stable coronary artery disease after 5.5 months of treatment (29). However, other studies reported that 6 months of statins therapy had no significant effect on coronary endothelial vasomotor function in patients with stable coronary artery disease (30,31). We studied the spasm segment as well as nonspasm segment in patients with coronary spasm, because no previous studies examined the effect of a statin on coronary spasm. It is interesting to note that the effect of a statin appears within 1 to 3 months of treatment in patients with unstable coronary syndrome, whereas it is apparent only after 1 to 2 years in those with stable coronary artery disease (8,9,32). Different pathophysiological mechanisms of coronary disease may thus respond differently to a statin.

Study limitations. Although the present study reveals that an addition of fluvastatin to the conventional therapy suppresses coronary spasm, the duration of the study period was short (6 months) and the number of the study subjects was small because of the invasive nature of the study for demonstrating coronary spasm. A larger number of patients and longer periods of follow-up would be required to determine the long-term efficacy and safety of a statin (fluvastatin) for the treatment of coronary spasm by using a noninvasive and more sensitive method for detection of coronary spasm. This study thus provides a rationale for the use of a statin for the treatment of coronary spasm. It is not yet known whether these combination therapies will prove to be cost-effective and safe for long-term use in patients with coronary spasm. We used fluvastatin because the risk for rhabdomyolysis and the possible drug interaction with a CCB were reported to be lowest and the possible vascular effect was highest among the statins clinically available at the time of initiating this study (33). It thus remains to be determined whether statins other than fluvastatin may have the similar effects on coronary spasm.

Conclusions

The present study showed that an addition of fluvastatin 30 mg/day to the conventional CCB therapy for 6 months significantly reduced coronary spasm induced by intracoronary injection of ACh as compared with the conventional therapy. The quantitative angiographic analysis revealed that fluvastatin was specifically effective in suppressing the vasoconstrictor response of the spasm segments as compared with the nonspasm segments.

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